Alarmins in tendinopathy: unravelling new mechanisms in a common disease

Neal L. Millar¹, George A. C. Murrell² and Iain B. McInnes¹

Abstract

Tendon disorders—tendinopathies—are the primary reason for musculoskeletal consultation in primary care in the UK and account for up to 30% of rheumatological consultations. While the molecular pathophysiology of tendinopathy remains incompletely understood, recent observations concerning repetitive stress and cellular load provide important mechanistic insight implicating a role for tissue alarmins. These in turn have an emerging effector role in many disease processes across the rheumatological diseases. Intracellular alarmins, also called damage-associated molecular patterns, are rapidly released following non-programmed cell death, are key effectors of the innate immune system and critically restore homeostasis by promoting the reconstruction of the affected tissue. Recent investigations have highlighted a key role for several alarmins including hypoxia-induced elements, cytokines and heat shock proteins affecting tissue rescue mechanisms in tendon pathology. This review aims to provide an overview of the biology of alarmins in the context of inflammatory mediators and matrix regulation in tendinopathy.

Key words: alarmins, tendinopathy, inflammation, cytokines, hypoxia.

Introduction

Primary disorders of tendons are common and account for a high proportion of referrals to rheumatologists and orthopaedic surgeons [1]. The most commonly involved tendons are the rotator cuff (particularly supraspinatus) in the shoulder, the forearm extensor (tennis elbow) and flexor tendons (golfer’s elbow) in the forearm, the patella tendon in the knee, the Achilles tendon in the lower leg and the tibialis posterior tendon in the ankle and foot. The intrinsic pathogenetic mechanisms underlying the development of tendinopathies are largely unknown; however, proinflammatory mediators, such as cytokines, have recently been functionally implicated in several model systems [2, 3]. Increasing evidence is emerging that repetitive tissue trauma and its associated damage in stromal tissues are recognized at the cell level via receptor-mediated detection of intracellular proteins released by necrotic or damaged cells [4]. The term alarmin is proposed to categorize such endogenous molecules that function to mobilize and activate immune cells after interaction with their specific receptors during host defence and tissue repair [4]. In this review, we summarize recent findings concerning the biology of key alarmins in inflammatory disease that may be important in the pathogenesis of primary tendon diseases.

Alarmins and inflammatory disease

Mammalian organisms have evolved intelligent systems to recognize certain molecules, or molecular patterns at the structural level, as danger signals. These in turn provoke rapid responses to life-threatening events, including cell damage, infection, burns and trauma. Classically, pathogen-associated molecular patterns (PAMPs) are a diverse set of microbe-derived molecules that alert organisms to intruding pathogens. Such exogenous PAMPs are recognized by cells of the innate and acquired immunity system, primarily through toll-like receptors (TLRs) that activate several signalling pathways, among which NF-κB is most distinctive [5]. Subsequently leukocytes are activated to destroy the pathogen and an immunological response is triggered in a cascade-type response. Alarmins are the equivalent of PAMPs but are endogenous molecules that are found in a variety of organelles in all cell types studied and maintain functions in normal cellular...
homeostasis. They are found in the nucleus as transcription factors [e.g. high-mobility group box–1 (HMGB1)], in the cytoplasm as calcium regulators (e.g. S100s), in exosomes as chaperones [e.g. heat shock protein (HSPs)] or as components of the cell matrix [e.g. hyaluronan] [6]. Although diverse in their locations during homeostatic conditions, alarmins share common functional characteristics. In addition to immune activation, an alarmin is released rapidly during necrosis, sequestered in apoptosis, has potential for active secretion by immune cells and ultimately promotes homeostasis [7]. Because alarmins are a diverse group of ubiquitous molecules implicated in nearly all inflammatory states, understanding and ultimately modulating their activity may provide novel avenues to control a variety of inflammatory processes.

HMGB1

HMGB1 was implicated as an important endogenous signalling molecule in 1999 when Wang et al. [8] described the cytokine activity of HMGB1 by identifying it as a late mediator of endotoxin-related lethality in mice. HMGB1 is released passively during cellular necrosis by almost all cells that have a nucleus and signals neighbouring cells to ongoing damage [9]. However, HMGB1 is also secreted actively by immune cells such as monocytes, macrophages and dendritic cells [8, 10] generally through non-traditional pathways that are not routed via the endoplasmic reticulum or Golgi apparatus, similar to IL-1 [11]. Stimuli for secretion of HMGB1 from immune cells are diverse and include PAMPs, cytokines and certain states of cellular stress [12]. There is ongoing debate as to whether tissue necrosis alone or in combination with cellular apoptosis also promotes HMGB1 release [13].

As an alarmin, HMGB1 potentially plays an important role in a wide variety of immunologically mediated conditions that range from sepsis to autoimmunity. Experimental models of arthritis including CIA or adjuvant-induced arthritis show significantly increased staining for HMGB1 in macrophage-like cells and vascular endothelial cells in synovial tissue [14]. Similar to findings in the animal models, aberrant extra nuclear HMGB1 expression in RA occurs in serum and synovial tissue and in the synovial fluid [15, 16] from patients with RA. Synovial fluid macrophages exhibit increased expression of receptor for advanced glycation end products (RAGE) and can be activated to release TNF–α, IL-1β and IL-6 by exposure to HMGB1 [16]. Others have found increased levels of HMGB1 in SLE [17], Sjögens syndrome [18] and polymyositis/dermatomyositis [19]. Thus, there is growing evidence that HMGB1 may play a pivotal role in the pathogenesis of a variety of inflammatory conditions and may present a new target of therapy of the same.

S100 proteins

S100 proteins are low-molecular-weight calcium-binding proteins ubiquitously expressed in vertebrates. The family constitutes 21 known members that are expressed in several tissues and cell types and play a major role in many cellular functions [20]. Uniquely, members of the S100 family have both intracellular and extracellular functions. Several members of the S100 family (S100A1, S100A2, S100A4, S100B, S100A9, S100A11 and S100B) have been identified in human articular cartilage, and their expression is upregulated in diseased tissue [21]. These S100 proteins elicit a catabolic signalling pathway via RAGE in cartilage and may promote progression of arthritis. S100A8 and S100A9 were initially identified in the context of RA [22]. Activated phagocytes expressing these S100 proteins are among the first cells infiltrating inflammatory lesions in inflamed synovium [23, 24]. In patients with active disease, S100A8/S100A9 is also expressed in macrophage-like cells within the lining layer, which show altered activation and differentiation under inflammatory conditions [22]. These proteins have also been shown in increased levels in PsA [25], SLE and dermatomyositis [26] presumably operating as tissue alarmins.

HSPs

HSPs are a family of highly conserved intracellular proteins that are found in all prokaryotes and eukaryotic cells. Although some HSPs are constitutively expressed, upregulation of expression is caused by exposure to a variety of cellular stressors, including heat shock, growth factors, inflammation and infection [27]. They promote cell survival by preventing mitochondrial outer membrane permeabilization, cytochrome c release, caspase activation and apoptosome assembly [28]. HSPs assist in general protein folding to prevent non-specific aggregation of misfolded or unfolded proteins, which would otherwise be rendered non-functional. Highly inducible HSPs such as HSP70 and HSP27 are transcriptionally controlled by heat shock transcription factor trimers, such as hsf1. For example, hsf1 represses transcription when bound to HSP70 during attenuation of the heat shock response as a negative feedback mechanism [29]. HSP activation can directly affect both innate and adaptive immunity, although controversial studies and varied opinions exist in the field [30–32]. The innate immune effector pathways induced by HSPs include cytokine and chemokine release and activation of NK cells [33]. Their expression in response to stress also has an important function in protection against apoptosis and in regulation of apoptotic cell signalling [34]. Thus, their evolutionary conservation and the upregulation during stress and binding to pattern recognition receptors make it logical that HSPs can act directly as danger signals for the immune system.

Cytokines

IL-1α and IL-33 are currently considered to be classical cytokine alarmins. IL-1α affects inflammatory and immune responses, angiogenesis and haematopoiesis [7, 35]. IL-1α is first synthesized as a precursor protein that is then activated via the protease calpain, which cleaves the IL-1α precursor into a mature 17-kDa form, liberating the 16-kDa N-terminal propeptide cleavage product (ppIL-1α). However, IL-1α secretion is rare from cells of mesenchymal origin and epithelial cells, such as keratinocytes, leaving intracellular IL-1α in its full-length precursor
form in these cells. Importantly, inflammatory responses to necrotic tissue in the absence of infection (i.e. ischaemia) are uniquely dependent on IL-1 receptor (IL-1R) signalling and due to IL-1α, not TLRs [6, 36]. Others have found that mesothelial cells respond in vitro to products of tissue necrosis with release of IL-1α [10]. Thus, IL-1α has both intracellular and extracellular functions in keeping with an archetypal alarmin.

**Fig. 1** The biology of alarmins in inflammatory disease.

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Receptor/s</th>
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<tr>
<td>HMGB-1</td>
<td>TLR2/TLR4/RAGE</td>
</tr>
<tr>
<td>HSP</td>
<td>TLR4</td>
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<tr>
<td>IL-1α</td>
<td>IL-1R</td>
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<tr>
<td>S100A8</td>
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<td>S100A9</td>
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<td>IL-33</td>
<td>ST2</td>
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Tissue damage/stress results in the release of alarmins which in turn signal via the highlighted receptor complexes. HMGB1 and IL-33 also have intracellular nuclear functions when upregulated. This results in the release of further cytokines, growth factors and changes in extracellular matrix production within the damaged tissue with pathological changes.
Interleukin 33, similar to IL-1β and IL-18, is a member of the IL-1 family that has a major role in innate immune responses driven through its receptor ST2. Initially described as nuclear factor of high endothelial venules by Baekkevold et al. [13] in 2003, Schmitz et al. [37] defined its function and role in the IL-1 family in 2005. This group identified the IL33 gene after searching a computational-derived database of the IL-1 family members where they found a ligand for the then orphan ST2 receptor. Interestingly, many reports define increased IL-33 in diseases with high numbers of necrotic cells such as RA and SLE [38, 39] but the mechanism/pathway whereby IL-33 is released in such disease states remains ill-defined. This has led to the suggestion that IL-33 acts as an alarmin. Thus, IL-33 may act in a similar manner to HMGB1 as both are released from dying cells and both are nuclear factors. Like HMGB1, IL-33 has also been shown to interact with heterochromatin and mitotic chromatin and is released from necrotic cells [40] while being actively retained complexed within chromatin of apoptotic cells.

Tendinopathy—a novel alarmin pathology

Overuse tendon injuries, namely tendinopathies, pose a significant, highly prevalent problem in musculoskeletal medicine [41] with the diagnosis and management of shoulder tendon injuries alone amounting to an annual cost of $3 billion to the US healthcare system highlighting the huge burden of disease [42]. The intrinsic pathogenetic mechanisms underlying the development of tendinopathies are largely unknown; however, excessive cellular load and repetitive stress have been shown to be functionally important in several models systems [43]. Thus, the pathological process implicating repetitive microtrauma or stress lends itself as a plausible alarmin-mediated pathology (Fig. 1).

Tendinopathy is an overuse injury, characterized by pain with movement, local tenderness, weakness and decreased mobility at the injured site. These symptoms are the result of deviation from the tendon’s normal physiology. In healthy tendon, 95% of tendon tissue is collagen I [44], synthesized by fibroblast-like tenocytes and integrated in the extracellular matrix with a variety of glycoproteins and glycosaminoglycans. Collagen III is mainly produced during tendon healing and remodelling, representing a rapid repair response, but intriguingly is biomechanically weaker than type I collagen. Macroscopically, tendons thicken and weaken in tendinopathy. Pathological degenerative changes are found in 90% of specimens of symptomatic tendon. In addition to mucoid, hyaline, hypoxic or fibrinoid degeneration at a histological level, collagen III is observed in symptomatic tendons at higher proportion than in uninjured tendons [45]. This indicates a disruption of tissue homeostasis, specifically excessive remodelling. Microscopically, collagen fibrils are disorganized with decreased tropocollagen cross-linking [46] and increased glycosaminoglycan production, both of which contribute to increased water retention and ultimately decrease in tensile strength (Table 1). Tenocytes become rounded and new blood vessels arise accompanied by neurogenesis. This increased neural volume is postulated to cause pain in tendinopathy [47, 48].

A human model of early tendinopathy

One of the major limitations of human studies is that tendon biopsies are usually obtained when patients are symptomatic and therefore biopsy material likely represents chronic rather than early phase disease [49]. A priori, we have considered that medical intervention at this early stage may offer considerable therapeutic advantage over later surgical approaches. We have previously demonstrated that matched subscapularis tendon from patients with full-thickness rotator cuff tears represents a model of early human tendinopathy [50] based on histological appearances and significantly increased levels of cytokines and apoptotic markers in these tissues (Fig. 2). These studies established a human model of early tendinopathy for the first time and have been independently confirmed [51]. This model has now not only allowed us to elucidate a role for alarmin molecules in tendinopathy but has finally allowed targeted mechanistic investigation into key molecular events in early tendon disease [11].

Table 1 Key pathological features of tendinopathy

<table>
<thead>
<tr>
<th>Findings</th>
<th>Macroscopic</th>
<th>Light microscopy</th>
<th>US findings</th>
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<tr>
<td>Normal tendon</td>
<td>Brilliant white</td>
<td>Organized parallel collagen bundles</td>
<td>Regular uniform fibre structure</td>
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<tr>
<td></td>
<td>Firm fibroelastic texture</td>
<td>Spindle shaped tenocyte nuclei</td>
<td>Parallel hyperechoic features</td>
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<td></td>
<td></td>
<td>Parallel nuclei alignment</td>
<td></td>
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<tr>
<td>Tendinopathy</td>
<td>Grey or brown</td>
<td>Disorganized collagen bundles</td>
<td>Local hypoechoic areas</td>
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<td></td>
<td>Thin tissue, fragile</td>
<td>Round dark-stained tenocyte nuclei</td>
<td>Irregular fibre structure</td>
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<tr>
<td></td>
<td>and disorganized</td>
<td>Increased number of nuclei with loss of parallel arrangement</td>
<td>Neovascularization on power Doppler</td>
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<td></td>
<td>Loose texture</td>
<td>Mucoid degeneration and vacuoles</td>
<td>Widening of tendon</td>
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<tr>
<td></td>
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<td>Increase of vascular and nerve ingrowth</td>
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<tr>
<td></td>
<td></td>
<td>Increased ground substance and GAG</td>
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Fig. 2 Key molecular events in tendinopathy.

**Early model of human tendinopathy**

(A) Anatomical depiction of biopsy sites within the shoulder highlighted by red circles. Biopsies taken from edge of torn suprasinatus tendon and intact subscapularis tendon in the same patient. Control tendon was obtained from patients undergoing arthroscopic stabilization with no evidence of a rotator cuff tear.

(B) The histological grades of tendinopathy in torn supraspinatus (n = 17), matched subscapularis (n = 17) and control subscapularis (n = 10) are shown. Grade 1 represents normal fibrotendinous tissue; Grade 2 represents mild-moderate degeneration with small increased prominence and roundness of the connective tissue and separation of the collagen fibres; Grade 3 represents advanced degeneration with mucoid ground substance and advanced fibrinoid degeneration and Grade 4 represents severe degeneration with mucoid ground substance, advanced fibrinoid degeneration and frank (continued)
Alarmins in tendinopathy

HSPs

Based on reports of excessive apoptosis in torn supraspinatus tendon and mechanically loaded tendon cells, we hypothesized HSPs may be present in rodent and human models of tendinopathy due to their central role in caspase-dependent apoptotic cell signalling [52]. We utilized a running rat supraspinatus tendinopathy overuse model with custom microarrays to investigate the process at a genetic level [53]. Additionally, torn supraspinatus tendon and matched intact subscapularis tendon samples (early pathology) were collected from patients undergoing arthroscopic shoulder surgery. Overall, 91 genes were found to be significantly upregulated, and 37 significantly downregulated in the running rodent model. The differential expression of apoptotic-related genes represented 6% (five genes) of the significantly upregulated genes and 8% (three genes) of significantly downregulated genes. Upregulation ($P < 0.01$) of HSP 27 ($\times 3.4$) and 70 ($\times 2.9$), cFLIP receptor ($\times 2.2$) and caspase 8 ($\times 3.1$) occurred in degenerative rat supraspinatus tendon subjected to daily treadmill running for 4 weeks. We further confirmed increased levels of HSP and apoptotic regulatory genes in human supraspinatus and subscapularis tendon at the RNA and protein level [54] (Fig. 2). Overexpression of HSP 27 is essential in preventing cells from undergoing apoptosis, a switch that may be redox-regulated [55]. HSP 27 inhibits specifically the cytochrome C and ATP-triggered activity of caspase 9 on the apoptotic pathway. Furthermore, HSP 27 indirectly interferes with cell death because of its ability to modulate intracellular glutathione [56], a parameter that is also regulated by exercise. Cytochrome C also triggers the oligomerization of Apaf-1, which in turn recruits pro-caspase 9 and pro-caspase 3 into the apoptosisosome (the caspase activation multiprotein complex). HSP 70 interacts with Apaf-1 thereby preventing its interaction with the caspases preventing apoptosis. HSP 70 also protects cells from heat stress [57], from the cytotoxic effects of TNF-α [58] and from nitric oxide [59]. Based on these observations, it would appear that HSPs act as a check point to apoptotic cell damage in tendinopathy.

Hypoxia

At a cellular level, a drop in oxygen concentration has two important consequences: activation of hypoxia-inducible factor-1 (HIF-1) and necrosis of cells that are distant from blood supply. HIF-1 is a heterodimeric protein composed of two subunits $\alpha$ and $\beta$. Under normoxia, HIF-1$\alpha$ is degraded by the ubiquitin–proteasome system, but when the intracellular oxygen concentration drops, HIF-1$\alpha$ is stabilized [60]. Following stabilization, HIF-1$\alpha$ translocates to the nucleus where it binds to HIF-1$\beta$. The HIF-1$\alpha$ and $-1\beta$ heterodimer activates the expression of vascular endothelial growth factors and their receptors, change in energy metabolism and upregulation of RAGE [61]. At the same time, necrosis causes release of intracellular alarmins (HMGB1 and IL33) that, by binding to different receptors NF-$\kappa$B, trigger the inflammatory response [62].

Hypoxic tendon injury has long been suggested as a cause of tendinopathy [63] although the exact mechanism remains to be defined. Hypoxic changes have been reported in tendon cells [64] and in the edge of tendon samples taken at the time of rotator cuff surgery [65]. However, the hypoxic changes may have occurred anywhere during the sequelae or pathology, rupture or after rupture and as such are difficult to define. The presence of hypoxia before rupture is supported by reports of increased lactate levels in Achilles tendinopathy compared with normal tendons [66] while recent in vivo work has shown decreased oxygen tension at the edge of torn rotator cuff sampled before surgical correction [67]. Increased vascularity has been demonstrated histopathologically [68] on Doppler US [47] and laser flowmetry [69]. However, the connection between hypoxia and changes in vascularity remains unclear with the contradictory element being that while hypoxia is a powerful stimulant to angiogenesis, impaired vascularity itself may ultimately lead to hypoxia.

*Fig. 2 Continued*

Chondroid metaplasia. Biopsies from subscapularis tendon revealed Grade 1–2 pathological changes in keeping with early tendinopathy. This was a chance finding when using this tissue as an internal control. This has subsequently allowed us to investigate alarmin molecule in early stressed tendon tissue. Inflammation in early human tendinopathy: (A) Immunohistochemical staining for mast cell tryptase positive staining in matched subscapularis tendon at cut edge (magnification $\times 100$). Black line represents $200\,\mu$m. (B) Relative expression of cell markers in human tendon samples. Histological scoring system, Grade 0: no staining, Grade 1: $<10\%$ cells positive, Grade 2: $10$–$20\%$ cells positive, Grade 3: $>20\%$ cells positive. Data displayed as mean $\pm$ S.E.M., $n = 20$ for supraspinatus and matched subscapularis, $n = 10$ for control group ($P < 0.01$, $P < 0.001$). These biopsies showed a large inflammatory infiltrate contrary to the belief that tendinopathy is not an inflammatory process. This has helped to link the alarmin molecules to tendinopathy due to their key role in the innate immune system. (C) The bar graph illustrates the relative expression of apoptosis genes in human tendon samples. The data are displayed as the mean $\pm$ S.E.M., $n = 17$ for supraspinatus (TSup) and matched subscapularis (MSub), $n = 10$ for control group ($P < 0.001$ between TSup/MSub and control; $P < 0.05$ between TSup and MSub). This revealed significant upregulation of heat shock proteins in torn and matched subscapularis tendon tissue highlighting alarmin pathology in early tendon disease.
We recently investigated the role of hypoxia in early human tendinopathy and thereafter explored mechanisms whereby tissue hypoxia may regulate apoptosis, inflammatory mediator expression and matrix regulation in human tenocytes [70]. Increased expression of HIF-1α, Bcl-2 and clusterin was detected in subscapularis tendon samples compared with both matched torn samples and non-matched control samples ($P < 0.01$). Hypoxic tenocytes exhibited increased production of proinflammatory cytokines ($P < 0.001$), altered matrix
Cytokines

Endogenous expression of various cytokines such as TNF-α, IL-1β, IL-6, IL-10, VEGF, and TGF-β has been also demonstrated in tenocytes [71–74]. Heat stress in tenocytes induced TNF-α but not IL-1β expression in equine tendon fibroblasts [75]. Increased amounts of IL-1α, IL-1β, TNF-α and IFN-γ were demonstrated in inflamed native equine tendon [76]. Mechanical factors also influence tendon cytokine profile whereby cyclic strain has been shown to induce VEGF expression in tenocytes [77] while stress deprivation lead to an overexpression of IL-1α and TNF-α and other cytokines such as TGF-β in the patellar tendon with subsequent mechanical deterioration of the tendon [78]. IL-1α is also known to effect the post-transcriptional regulation of collagen synthesis. As this is a pathological feature of tendinopathy, it promotes the notion of IL-1α as an alarmin capable of extracellular matrix signalling.

We have recently investigated the expression of IL-33 and its receptor ST2 in tendon biopsies. Subscapularis tendon samples exhibited significantly greater staining for IL-33 and ST2 compared with either matched torn supraspinatus samples or control tissue (unpublished data). Nuclear staining was detected in endothelial cells, but also weak staining of IL-33 was noted in the cytoplasmic compartment. In contrast to IL-33 and ST2, which were found at lower levels in control tissue, IL-1RacP was noted to be expressed at high levels in normal healthy tendon compared with both IL-33 and ST2 expression, which may represent the enhanced ability of normal tendons to respond to IL-33 signalling. This increased expression, was confirmed at the mRNA level confirming local cellular synthesis. Additionally, we were able to induce IL-33 production in tenocytes in vitro similar to that reported in synovial fibroblasts [79]. Thus, it appears that IL-33 may be an important early signal in stressed tendon and more detailed mechanistic investigation is currently underway to determine any downstream matrix effects.

Summary

In conclusion, alarmins are components of the natural tissue response that can act in a positive or negative manner to integrate host immune system function with tissue homeostasis during the course of disease. These molecules act particularly as early regulators of the decision of a tissue/cell towards a reparative versus degenerative/inflammatory pathological process in joint-related diseases. Repetitive microtrauma or stress is now considered one of the main pathophysiological causes of tendinopathy. Our investigations into early tendon damage have revealed a role for a number of alarmins. We propose that when these molecules are released from stressed tenocytes, they act as orchestrators of both the tissue healing response and the subsequent inflammatory reaction with a fine balance between reparative versus degenerative change (Fig. 3). Further work is ongoing within our institute to further elucidate their mechanistic role and possible therapeutic targeting. In particular, we propose that early and aggressive medical management of such conditions, based on plausible pathological mechanisms, may subvert progression to chronicity and hence the need for future surgical intervention.

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Clinical vignette

Fibro-osseous pseudotumour of the digit in a patient with rheumatoid arthritis

A 61-year-old woman had been treated with methotrexate for a seropositive and erosive rheumatoid arthritis since 2001. In November 2011 she developed a painless inflammatory tumefaction of the right index finger. She did not report any previous trauma or wound. Standard biology and initial X-rays were normal. Ultrasound analysis and MRI (Fig. 1A) showed inflammatory soft tissue oedema and bone marrow oedema of the middle phalanx.

A profound skin biopsy was performed. Bacteriological investigations were negative. Histology showed non-specific oedema of soft tissues without inflammatory infiltrate. One month later the volume of the tumefaction increased (Fig. 1B). A control X-ray showed periosteal calcifications around the middle phalanx (Fig. 1C). A surgical bone biopsy was performed, but histology was again non-specific, showing non-inflammatory necrotic and fragmented bone. Two months later, in the absence of an aetiological diagnosis, amputation of the finger was carried out. Definitive histology (Fig. 1D) described a periosteal centrifuge neo-osteogenesis consisting of focal irregular trabeculae with osteoid formation and osteoblastic rimming, evocative of fibro-osseous pseudotumour. This is a rare, non-malignant heterotopic ossifying lesion involving the subcutaneous tissues of the digits. The treatment of choice is, when possible, conservative complete excision of the lesion, leading most of the time to complete recovery [1].

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Fig. 1 Fibro-osseous pseudotumour of the index finger.

(A) MRI of the right index finger showing inflammatory soft tissue oedema and bone marrow oedema of the middle phalanx; (B) clinical aspect; (C) X-ray 1 month after the beginning of symptoms; (D) histopathology showing periosteal centrifuge neo-osteogenesis.

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Reference